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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BOARD OF PATENT APPEALS AND INTERFERENCES

Attorney Docket No. 18733/808

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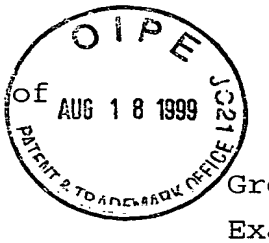

In re patent application of
David M. GOLDENBERG
Serial No. 08/949,758 Group Art Unit: 1646
Filed: October 14, 1997 Examiner: P. Mertz
For: NON-ANTIGENIC TOXIN-CONJUGATE AND FUSION PROTEIN OF INTERNALIZING RECEPTOR SYSTEM

APPELLANTS' BRIEF UNDER 37 CFR §1.192

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

This brief is in furtherance of the Notice of Appeal filed in this case on June 18, 1999. The fees required under 37 CFR §1.17(f) and for the petition for extension of time are included in our Check No.071138. Any fee deficiency or overpayment may be charged to our Deposit Account 19-0741.

This brief is transmitted in triplicate in conformance with 37 CFR §1.192(a).

I. Real Party in Interest

The real party in interest in this case is IMMUNOMEDICS, INC., as evidenced by an assignment recorded on March 24, 1998, at Reel 9068, Frame 0966.

II. Related Appeals and Interferences

There are no related appeals or interferences known to appellant, the appellant's legal representative, or the assignee which will directly affect or be directly

affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims

1. Claims canceled: 2
2. Claims pending: 1, 3-21
3. Claims withdrawn from consideration: 16-19 and 22
4. Claims objected to, but allowable: 2-5
5. Claims rejected: 1, 6-15, 20 and 21
6. Claims on appeal: 1, 6-15, 20 and 21

IV. Status of Amendments

No claim amendments were made following final rejection, and all claim amendments have been entered into the record.

V. Background and Summary of the Invention

The present invention relates to a fusion protein of a component of an internalizing receptor system and a moiety that binds to a specific cellular surface marker on a cell, to a conjugate of a non-immunogenic RNase toxin and a ligand for the internalizing receptor system, and to a method of tumor therapy using the conjugate and internalizing receptor system.[1]

There is now a fairly large and growing body of experience in the use of monoclonal antibodies (mAbs) for the therapy of lymphoma. Several studies targeting different B-cell restricted CD (clusters of differentiation) antigens have shown promising results. These studies have used radiolabeled mAbs and, to a lesser

[1] Specification at page 1, and claims 1 and 8.

extent, mAb-toxin conjugates, and have targeted CDs19-22, CD37, and HLA-DR.

MAbs used in lymphoma therapy differ in their ability to bind cognate antigen and to become internalized. For example, CD22 exhibits efficient internalization as well as reexpression of antigen after internalization. It suffers, however, from relatively low expression levels on most B-cell malignancies, and is not widely expressed, *e.g.*, it is expressed on only 30-50% of cases of B-cell lymphocytic leukemia (B-CLL).

The present inventor has studied an anti-CD22 mAb, LL2. Preliminary studies using LL2 labeled with ^{131}I for both therapy and imaging of NHL have produced response rates of 30-90+%, with varying percentages of complete responses and differences in durability of response. Higher response rates and longer disease-free survival have been associated with higher total doses of antibody and of radioactivity, which usually have required autologous bone marrow or peripheral stem cell rescue. While the results are encouraging, it is desired to increase therapeutic efficacy and decrease toxicity, particularly myelotoxicity.[2]

The CD20 antigen, in contrast to the CD22 antigen, is a quite highly expressed B-cell restricted antigen that is expressed on a wide range of B-cell malignancies, ranging from acute lymphocytic leukemia (ALL) to the more differentiated B-Cell (B-CLL) and non-Hodgkin's lymphoma (NHL), and even to hairy cell leukemia (HCL). It

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[2] Specification at page 1.

generally is expressed on cells in the vast majority of cases of these malignancies at a high antigen density. A major disadvantage of CD20 is that it is a slowly internalizing antigen. For radioimmunotherapy (RAIT) directed against CD20, this feature may not be a problem, but it militates significantly against the use of CD20 for toxin-based therapy.[3]

A further problem of CD20 is the fact that B-cell malignancies exhibit a more rapid dissociation of bound anti-CD20 mAbs from the surface as compared to nonlymphoma tumor cells. This suggests that a therapy that uses bonding to a B-cell restricted antigen, particularly those characterized by slow internalization, would not be successful.

A variety of mAb-toxin constructs have been tested in both *in vitro* experiments and human trials. These studies have demonstrated potent and specific effects of these reagents. Most of the toxin molecules that have been used derive from either plant or bacterial sources and hence produce allergenic sensitization in patients. This severely limits the duration of therapy.

While major progress has been made in the therapy of B-cell malignancies such as NHL and B-CLL, there remain a substantial number of patients with B-cell malignancies who exhibit primary resistance to, or relapse after, optimal chemotherapy. A therapy that is effective over long periods of time in most or all patients with B-cell malignancies is provided by the present invention, which

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[3] Specification at pages 1-2.

improves the value as antigenic targets of slowly internalizing surface antigens such as the CD20 antigen, and overcomes the tendency of antibodies bound to the surface of lymphoma cells to dissociate rapidly from the surface of the cells.[4]

In accordance with the present invention, the value of surface antigens as antigenic targets can be improved significantly by functionally linking them to a high affinity, internalizing receptor system. The present invention is of particular advantage in the case of surface antigens that do not internalize or that internalize slowly. A preferred example of a high affinity, internalizing receptor system is the IL-15 receptor system. When the IL-15 receptor system is used, it can be employed with all malignant cells that contain the β/γ_c chains of IL-15 receptor. The presence of β/γ_c chains of IL-15 on the cells provides the basis for a continuously internalizing receptor system that can be bridged to a surface antigen, particularly a slowly internalizing antigen, by way of a bispecific fusion protein and cognate ligand.[5]

The present invention allows increased intracellular delivery into the malignant cell of cytotoxic ligands. It also improves methodologies in which a radionuclide is used as a therapeutic agent, by producing a tighter binding of the radionuclide to the malignant cell and by reducing dissociation of the targeting agent from the cell surface.

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[4] Specification at page 2.

[5] Specification at pages 3-4.

In accordance with the present invention, malignant cells are pretargeted with a fusion protein. The fusion protein comprises a region of IL-15α, preferably an extracellular domain, and a bispecific antibody or antibody fragment that has a first specificity for a cell marker specific to a malignant cell marker and a second specificity for the region of IL-15α. The fusion protein is positioned on the malignant cells by means of the surface antigen expressed by the malignant cells. In an alternative embodiment, the fusion protein is formed *in situ*, by first administering the bispecific antibody, and then administering IL-15α which binds to the bispecific antibody that is already bound to the malignant cells. In either case, addition of an armed ligand comprising IL-15 ligand armed with an immunogenic RNase or with a therapeutic radionuclide then results in the formation of a trimeric complex of the β/γ_c chains of IL-15 receptor, in which the α-chain of IL-15 receptor is attached to the surface antigen and IL-15/RNase toxin and/or therapeutic radionuclide conjugate. Alternatively, both the fusion and the trimeric complex can be formed *in situ*. This leads to rapid internalization of RNase toxin and/or therapeutic radionuclide into the malignant cells. While internalization is not necessary for a therapeutic radionuclide to be effective, the trimeric complex provides a tighter binding to the malignant cells, and thus improves these modalities as well. The present invention can be used as therapeutic reagents for treating leukemias and lymphomas.[6]

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[6] Specification at page 4.

VI. Issues

There are two issues on appeal in the present case. The first is whether claims 8-15 are enabled under the first paragraph of 35 USC §112. The second is whether claims 1, 6 and 7 are anticipated under 35 USC §102(b) by Mallinckrodt Medical, Inc.

VII. Grouping of Claims

For purposes of this appeal, the claims do not all stand or fall together, but will be argued separately according to the following groupings:

Group 1 Claims 8-11 and 13-15
Group 2 Claim 12
Group 3 Claims 1, 6 and 7

For appellants' position on the patentability of Group 1, see Section IXA. For appellants' position on the separate patentability of Group 2, see Section IXA, last paragraph. For appellants' position on the separate patentability of Group 3, see Section IXB.

VIII. Summary of the Argument

The specification fully enables a fusion protein comprising a bispecific antibody that has a first specificity for a cell marker specific to a malignant cell and a second specificity for a region of IL-15α. However, applicant's therapy, like so many others, does not require "selective killing of malignant cells without killing those cells (expressing specific markers), that are required for normal function of the immune system," as alleged, and the Examiner has not met her burden of establishing lack of enablement.

Mallinckrodt Medical, Inc. does not disclose a conjugate of a non-immunogenic RNase or therapeutic radionuclide and a cell-specific cytokine. The use of "too much" radionuclide, such that a therapeutic effect might occur, is not fairly taught by the reference.

IX. Argument

A. The specification fully enables a fusion protein comprising a bispecific antibody that has a first specificity for a cell marker specific to a malignant cell and a second specificity for a region of IL-15α

Claims 8-15 are rejected as lacking enablement under the first paragraph of §112. The Examiner finds that the specification enables a fusion protein comprising a bispecific antibody that has a first specificity for CD20 and a second specificity for a region of IL-15α, but contends that the specification does not enable a fusion protein comprising a bispecific antibody that has a first specificity for a cell marker specific to a malignant cell and a second specificity for a region of IL-15α. In this regard she argues that "there are no specific cell markers known that are specific to malignant cells,"[7] and that in order to practice the invention the artisan would have to know how to deliver the therapeutic agent so that it would not kill non-malignant cells, more particularly so that it would not destroy the normal function of the immune system.

Cancer therapy using antibodies to antigens expressed on malignant cells, such as the LL2 anti-CD22 mAb, is a widely-accepted therapeutic approach. For

[7] Official Action dated September 28, 1998, at page 4.

example, the present specification references "a fairly large and growing body of experience in the use of monoclonal antibodies (mAbs) for the therapy of lymphoma," including the use of different B-cell restricted CDs (clusters of differentiation). More particularly, preliminary studies using LL2 labeled with ^{131}I for both therapy and imaging of NHL have produced response rates of 30-90+%, with varying percentages of complete responses and differences in durability of response.

While it is true that antibodies such as LL2 also will bind to non-malignant cells, binding is much higher for malignant cells. This is so because the malignant cells express the cognate antigen much more highly than do non-malignant cells. This is supported by Verheul, previously cited by the Examiner, which discusses "tumor therapy whereby the receptor on the cell surface is ***specific*** for tumor cells ***or at least is preferentially expressed by said tumor cells***."[8] By merely managing the dose, it often is possible to kill malignant cells without unduly damaging non-malignant cells.

In cases where higher doses are necessary to kill the malignant cells, adjunct therapy with cytokines and/or autologous bone marrow or peripheral stem cell rescue can be used as part of an effective therapy. Again, Verheul notes that "antisera directed against the entire lymphocyte population...have been shown to be useful in for instance kidney transplantations (1,2), in spite of the fact that the patient is temporarily immuno-

[8] Verheul at page 1, third paragraph.

incompetent."[9] This directly addresses the Examiner's contention that a therapy must not "[kill] those cells (expressing specific markers), that are required for normal function of the immune system."[10] The more desperate the circumstances, the more "acceptable" the adverse side effects associated with a therapy. A lack of enablement rejection should not be sustained in the face of evidence that such side effects are deemed acceptable in conventional therapies. Accordingly, one of ordinary skill in the art is clearly able to practice the present invention.

The Examiner has noted applicant's argument that there is a large and growing body of experience in the use of antibodies to antigens expressed on malignant cells, such as the LL2 anti-CD22 mAb, to treat cancer, but has not countered applicant's position that absolute specificity is not necessity. Instead, she has indicated that she would maintain the enablement rejection "unless Applicants can show differences in expression of cell markers specific to malignant cells, and selective killing of malignant cells without killing those cells (expressing specific markers), that are required for normal function of the immune system."[11] Applicant has provided factual reasons why the relatively low doses enabled as a result of the higher binding to malignant cells as a result of greater expression of the antigens in question, coupled when necessary with adjunct therapy with cytokines and/or autologous bone marrow or peripheral stem cell rescue,

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[9] Verheul at page 1, paragraph 5.

[10] Official Action dated February 18, 1999.

[11] Official Action dated February 18, 1999.

allows effective therapy. Applicant has also referenced successful clinical applications based on such therapies. Applicant's therapy, like so many others, does not require "selective killing of malignant cells without killing those cells (expressing specific markers), that are required for normal function of the immune system." The Examiner has not met her burden of establishing lack of enablement.

Claim 12 recites a fusion protein comprising a bispecific antibody that has a first specificity for CD20 and a second specificity for a region of IL-15α. Inasmuch as the Examiner has found that the specification enables a fusion protein comprising a bispecific antibody that has a first specificity for CD20 and a second specificity for a region of IL-15α,[12] the inclusion of claim 12 in the rejection for lack of enablement is improper on its face.

B. Mallinckrodt Medical, Inc. does not disclose a conjugate of a non-immunogenic RNase or therapeutic radionuclide and a cell-specific cytokine

Claims 1, 6 and 7 stand rejected under §102(b) based on Mallinckrodt Medical, Inc. The Examiner urges that Mallinckrodt Medical, Inc. disclose conjugates with IL-2 and "teach a conjugate of a therapeutic radionuclide and a cell-specific cytokine." The Examiner is incorrect in alleging that Mallinckrodt Medical, Inc. "teach a conjugate of a therapeutic radionuclide and a cell-

[12] Official Action dated September 20, 1999, at page paragraph 4.

specific cytokine."[13] To the contrary, Mallinckrodt Medical is directed to "a labelled CXC chemokine [utilized] to ***image*** a target site in an animal's body" and does not suggest conjugates with a ***therapeutic*** radionuclide. In this regard, the document details the "several *a priori* advantages for clinical nuclear imaging" that are provided by IL-8."[14]

The disclosure in Mallinckrodt Medical, Inc. of "a labelled CXC chemokine [utilized] to ***image*** a target site in an animal's body" does not encompass, or even suggest, conjugates with a ***therapeutic*** radionuclide. The Examiner argues, however, that "a labeled CXC chemokine with a radioactive agent as a label to be used as a diagnostic, ***can be therapeutic if too much of the radionuclide conjugated to said cytokine is used***.[15] The only radionuclides disclosed in Mallinckrodt Medical are I-125, Tc-99m, and In-111.[16] All of these radionuclides are useless for therapy, *i.e.*, even were a large amount of radionuclide-labelled conjugate to be used, a therapeutic effect would not ensue. Moreover, Mallinckrodt Medical, Inc. specifically teaches the use of "***a diagnostically effective dosage***" which will "vary depending on

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[13] The Examiner also is incorrect in her allegation that Mallinckrodt Medical, Inc. discloses conjugates with a cytokine "such as IL-2." Mallinckrodt Medical, Inc. only discloses conjugates with IL-8, and not with IL-2. Furthermore, the list of cytokines bridging pages 2 and 3 (cited by the Examiner) does not include IL-2.

[14] Mallinckrodt Medical, Inc. at page 26, lines 15-16.

[15] Official Action dated February 18, 1999, at page 4, emphasis added.

[16] Mallinckrodt Medical, Inc. at page 5, lines 9-11.

considerations such as age, condition, sex and extent of disease in the subject individual, counter indications, if any, and variables."[17] ***The use of "too much" radionuclide, such that a therapeutic effect might occur, is not fairly taught.*** The Examiner's allegation that Mallinckrodt Medical anticipates the subject matter of claims 1, 6, and 7 is not well taken.

X. Conclusion

For these reasons, the Board is respectfully requested to reverse the Examiner and remand this application for issuance.

Respectfully submitted,

Aug. 18, 1999
Date

Bernhard D. Saxe
Reg. No. 28,665

FOLEY & LARDNER
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
(202) 672-5300

[17] Mallinckrodt Medical, Inc. at page 10, lines 12-16, emphasis added.

APPENDIX: APPEALED CLAIMS

1. A conjugate of a non-immunogenic RNase or therapeutic radionuclide and a cell-specific cytokine.

6. A composition comprising a conjugate according to claim 1, and a pharmaceutically acceptable carrier.

7. A composition as claimed in claim 6, additionally comprising a diagnostic radionuclide conjugated to said cytokine.

8. A fusion protein comprising a bispecific antibody that has a first specificity for a cell marker specific to a malignant cell and a second specificity for a region of IL-15α.

9. A fusion protein as claimed in claim 8, wherein said bispecific antibody is a scF_v.

10. A fusion protein as claimed in claim 9, wherein said scF_v is a fusion of two individual scF_v molecules.

11. A fusion protein as claimed in claim 8, wherein said cell marker is a B-cell restricted antigen.

12. A fusion protein as claimed in claim 11, wherein said cell marker is CD20.

13. A fusion protein as claimed in claim 8, wherein said region of IL-15α is an extracellular domain of IL-15α.

14. A composition comprising a fusion protein according to claim 8 and a pharmaceutically acceptable carrier.

15. A kit comprising a conjugate of an RNase and IL-15, and a fusion protein comprising a bispecific antibody that has a first specificity for a cell marker specific to a malignant cell and a second specificity for a region of IL-15α.

20. A fusion protein as claimed in claim 8, wherein expression of said cell marker on said malignant cells is higher than expression of said cell marker on non-malignant cells.

21. A kit according to claim 15, wherein said RNase is onconase.

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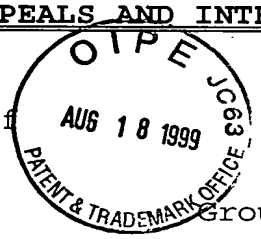

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BRIEF ON APPEAL

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